Running a High-throughput screen at the UCB Drug Discovery Center

Welcome to the the UC Berkeley Drug Discovery Center. This document outlines the guidelines for running a HTS screen with the Center. We operate as a freestanding unit using a collaboration model, not as a recharge "core". We provide state-of-the-art technology and scientific expertise in assay development, screening, target ID, drug discovery through preclinical development and IND submission, and grant writing.

Screening process

Initial Consultation: Potential collaborators are invited to discuss a screening idea with the DDC team. We'll discuss the target of interest, screening modalities and assay adaptation to HTS if needed. Once assay development is underway, the Graduate student or postdoc will be matched with an DDC scientist, who will consult during assay development and lead the screen.

***Assay development*:** The initial assay is developed by the initiating lab, usually in their laboratory. Clients are welcome to use DDC instrumentation with guidance from DDC staff to test their assay development. Ideally we would like to see:

- DMSO tolerability up to 2% (v/v)
- assay should be homogenous and be running at room temperature
- stability of reagents at room temperature over 8h
- Timecourses/binding kinetics as applicable to understand rate-limiting step for activators, affinities and relative concentrations of components
- If there is a positive control, it should be used to assess window of activation/inhibition under different assay conditions and compared to published data for potency
- assay miniaturized to 384 well format, equal volume addition 12.5ul+12.5ul for enzyme and substrate reagents
- conform to 25ul/well, with a final compound concentration at 40uM and 2% DMSO (v/v)
- z' determined from 20 wells of positive control (if available), 20 wells of negative control on DDC reader in the type of plate used for assay
- Whole plate experiment with DMSO control on DDC reader in the type of plate used for assay so that plate effects can be seen and eliminated if needed
- Availability of counterscreen / control assay for confirmation level (384 well) and follow-up paradigm in low throughput /benchtop assays

Not all assays will conform to these guidelines and there is flexibility around most points, but it takes time and increases cost to accommodate.

Primary screen: We have the following libraries available: 1) FDA-Approved drug library that can be used for a pilot screen or drug repurposing, 1,200 compounds; 2) Bioactive compound library, well characterized in preclinical and clinical models, targets known; 4,170 compounds; 3) Antibacterial diversity library: Enriched for predicted antibacterial activity using computational methods, 15,000 compounds; 4) Diversity library, drug like, diverse molecules with no IP attached when we bought them; 100,000 compounds. The entire library is composed of 120,370 compounds. We will typically start with FDA-Approved library and then move through the rest. Smaller screens can be done as needed with the sublibraries, but if we follow up individually in confirmation and dose response it will add to allover cost – most efficient to screen entire library and then run confirmation and dose response only once for the best hits.

***Data analysis*:** Data is uploaded and analyzed in CDD vault analysis servers. Data will be kept confidential and each project is accessible only to approved users.

***Confirmation and dose response*:** Hits are cherry-picked for rescreening in a confirmation run along with a potential orthagonal assay to remove false positives, Typically 0.3-0.5% of compounds screened are cherry-picked at 2 µL and plated at 40 µM. Testing will be done in original and control/orthogonal assays and hits will be clustered by similar substructures. Team discussion will be used to identify which compounds to move forward. A subset of the confirmed hits are then run in a 10 point dose response.

***Preliminary SAR*:** HTS data are analyzed by substructure or other similarity algorithm to determine preliminary structure-activity relationships (SAR). SAR can be used to focus compounds for repurchase and/or for generating hypotheses about the binding site.

Resupply: The UCBDDC will provide information on repurchasing the active compounds. The initiating CBDDC will suggest alternatives, such as close analogs that are commercially available. Further testing can be facilitated as needed.

Final report: Collaborating laboratory will be receiving a final report of compounds including structures, dose response curves, and confirmation and control data as well as cluster information.

Cost sharing: as a collaborator, we make equipment and libraries available for free at this time, but expect a cost-share for the part of Eddie's time actually used on the project. Also all reagents, plates and supplies needed for the project will be purchased by the collaborating laboratory. The work performed will generally warrant co-authorship on publications and patents.

Grants and proposals: we are happy co-author grant proposals for joint projects and have a grant writer, Dr. Celine Perier, who can write a first draft. If we have a joint grant and screen can be financed through that, no other cost-share from the PI is necessary for the project.

The more we can collaborate on grants the better for our long-term viability as we do not receive institutional funding and are **100% philanthropy backed**. Our goal is to provide screening and translational science expertise to the campus community at a reasonable price. New equipment or libraries can only be acquired through grant funding. **Please keep us in mind if you come across an opportunity that could benefit from a screening / translational science component!**

Infrastructure:
State of the art liquid handling and compound management infrastructure for library stamping and generation of confirmation and dose response plates in 384 well format (96 well possible if needed). Data analysis and visualization software integrated with compound structures. Supported readouts include Absorbance, fluorescence, luminescence, alpha-screen, and microscopy. Others possible – please inquire.

Team:

Dr. Julia Schaletzky, Executive Director
A Harvard-trained biochemist, with more than 10 years biotech industry experience. Specializing in preclinical research and development, including High-throughput screening, assay development and in vitro pharmacology. Drug Discovery expert, Instructor for the "Biology&Business" program (collaboration between MCB and Haas school of business), expertise in translational science, entrepreneurship, startup formation and fundraising.

Eddie Wehri, Screening Scientist
Industry veteran with more than 20 years experience, screening expert and automation specialist, lab manager for the DDC. Eddie will be executing the screening project on DDC equipment, analyse data and assist with early assay development that requires our instrumentation.

Dr. Celine Perier, Grant writer
Dr. Perier is a trained neuroscientist with international experience in Paris, Barcelona and New York. She has studied the role of mitochondria in Parkinson's disease pathogenesis with a particular focus on the molecular mechanisms of neuronal dysfunction/death in neurodegenerative disorders in order to try to find a cure for this group of disabling, currently incurable diseases. She is passionate about science communication and believe that scientific storytelling is a crucial element for the advancement of science.